

Memorandum to File**Pharmacology/Toxicology, Division of Nonprescription Drug Products****Reviewer: D. Charles Thompson, RPh, PhD, DABT**

TSI: 1355	Sponsor: Multiple
Drug: Acetaminophen (APAP)	Indication: Pain, fever

Subject: TSI 1355: Review of Nonclinical Published LiteratureBackground

A new Track Safety Issue (TSI-1355) was opened on 1 April 2014 following a report by Cooper et al. (JAMA Pediatr. 168(4):306-7, 2014) suggesting a possible link between APAP use in pregnant women and the development of attention-deficit/hyperactivity disorder (ADHD) in their offspring. Subsequent CDER/OSE investigation of the issue (Epidemiology Review, A.D. Mosholder, 18 March 2015) identified two additional clinical reports of a potential association but concluded that “Whether the association is causal in nature remains uncertain.” It was recommended that “The existing preclinical data on pregnancy exposure to APAP and exposure of juvenile animals to APAP regarding neurodevelopment should be assessed.” This memorandum is intended to address OSE recommendations.

Review and Evaluation of Nonclinical Published Literature

Initially, internal consultation was undertaken with DPP (Ikram M. Elayan, Ph.D.) to frame the scope of the search. It was confirmed that validated animal models for ADHD do not exist at this time. Nonclinical data that would likely have the highest probability of addressing the question at hand would be adequately designed and conducted pre-/postnatal studies, as well as studies in very young juvenile animals ($\leq$ PND-7), in which adequate neurobehavioral/learning and memory endpoints have been assessed. However, what behavioral responses in animals are most likely to be predictive of an ADHD response in humans are uncertain.

Subsequently, it was determined that nonclinical data on APAP published through 2010 in the peer reviewed literature have recently been reviewed internally in support of labeling for a number of NDA applications in DAAAP.¹ While a number of identified reports evaluated developmental and reproductive effects of APAP generally, only a continuous breeding study conducted in mice by the National Toxicology Program (NTP)² included pre- and postnatal developmental data. It was concluded that “...this study did not include comparable endpoints as a dedicated pre- and postnatal development study.” No data were identified in the DAAAP review that discussed developmental effects potentially of relevance to the question at hand.

This memorandum, therefore, focuses on a review of reports published from 2010 through the present and identified via searches of the National Library of Medicine’s

¹ For example, see: NDA 21-123: Nonclinical Labeling Review, R.D. Mellon, Ph.D., 12 November 2013; NDA 22-450: Supervisor’s Secondary Review-Pharmacology/Toxicology Review and Evaluation, R.D. Mellon, Ph.D., 10 February 2010.

² Reel et al. Fundam Appl Toxicol 18:233-239, 1992.

PubMed and TOXNET/DART databases, using the search term, 'acetaminophen' (including synonyms and CAS numbers). Studies that appeared by abstract and/or title to involve prenatal and/or early postnatal APAP exposure in animals and to assess effects on neurobehavioral/learning and memory endpoints were very limited and are summarized in the following paragraphs.

Viberg H, Eriksson P, Gordh T, Fredriksson A. Paracetamol (acetaminophen) administration during neonatal brain development affects cognitive function and alters its analgesic and anxiolytic response in adult male mice. *Toxicol Sci.* 2014 Mar;138(1):139-47.

Male NMRI mice (Sweden) were administered APAP via SC injection on PND-10 (corresponding approximately to a term infant human at birth) either as a single dose (30 mg/kg) or repeated doses (30 + 30 mg/kg, 4hr apart). This dose corresponds to a human equivalent dose (HED) of approximately 2.4-4.9 mg/kg based on BSA scaling. The maximum recommended daily dose in children under 12 years of age is 75 mg/kg in divided doses. Animals (6-9/group) underwent assessments for brain concentrations of APAP and brain-derived neurotrophic factor (BDNF) at 1 to 24 hours after dosing. A battery of behavioral tests was performed beginning at 2 months of age with a 1-week separation between tests. Testing included assessments of spontaneous behavior (locomotion, rearing, and total activity), radial arm maze (spatial learning), hot plate (analgesic efficacy), and elevated plus maze (anxiety-like behavior).

Results indicate that APAP levels in brain peaked at 1 hour after dosing and had dropped significantly by 2 hours; BDNF levels were significantly elevated in frontal cortex regions by 24 hours in APAP-exposed animals versus saline controls. Behavioral assessment findings indicate "...altered locomotor activity on exposure to a novel home cage arena and a failure to acquire spatial learning in adulthood, without affecting thermal nociceptive responding or anxiety-related behavior." However, high-dose mice failed to exhibit APAP-induced "...antinociceptive and anxiogenic-like behavior in adulthood." The investigators suggest that such "...behavioral alterations in adulthood may, in part, be due to [APAP-induced] changes in BDNF levels in key brain regions at a critical time during development."

While these results are suggestive and warrant further investigation, they are limited in their ability to address the question at hand in that the study design did not incorporate prenatal exposure or exposure of juvenile animals of ages corresponding to human prenatal exposure. In addition, the justification for the selected dose levels was not adequate, given that the administered dose appeared to be less than maximal based on typical BSA scaling factors and approved dosing levels for APAP in children under 12 years. Also, the animal numbers employed and the endpoints evaluated in the study design were not adequate in comparison with Agency guidance for pre-/postnatal and juvenile animal study designs.

Blecharz-Klin K, Joniec-Maciejak I, Jawna K, Pyrzanowska J, Piechal A, Wawer A, Widy-Tyszkiewicz E. Effect of prenatal and early life paracetamol exposure on the level of neurotransmitters in rats-Focus on the spinal cord. Int J Dev Neurosci. 2015 Dec;47(Pt B):133-9.

Blecharz-Klin K, Joniec-Maciejak I, Jawna K, Pyrzanowska J, Piechal A, Wawer A, Widy-Tyszkiewicz E. Developmental exposure to paracetamol causes biochemical alterations in medulla oblongata. Environ Toxicol Pharmacol. 2015 Sep;40(2):369-74.

In these two parallel reports from the same Polish laboratory, male Wistar rats were exposed to APAP indirectly during gestation and lactation and then directly from weaning until the end of the second postnatal month. Three groups of pregnant females (n=10/group) were randomized to either tap water control or APAP at a dose of 5 or 15 mg/kg, administered via the drinking water. Following termination of dosing at PND-60, the reports describe assessment of tissue levels of a battery of monoamine and amino acid neurotransmitters and their metabolites via HPLC in, respectively, thoracic spinal cord and medulla oblongata samples. While in both reports, statistically significant differences between control and APAP-exposed animals were noted in multiple analytes, the clinical relevance of these findings is unclear, specifically as they relate to addressing the question at hand.

Isling LK, Boberg J, Jacobsen PR, Mandrup KR, Axelstad M, Christiansen S, Vinggaard AM, Taxvig C, Kortenkamp A, Hass U. Late-life effects on rat reproductive system after developmental exposure to mixtures of endocrine disrupters. Reproduction. 2014 Mar 2;147(4):465-76.

This report, while involving perinatal exposure to APAP, did so—similarly to several other reports not discussed here—as part of a mixture with other endocrine-disrupting toxicants. Four groups of 14 time-mated Wistar rats were exposed by gavage from GD-7 to PND-22 to a mixture of 13 purported anti-androgenic and estrogenic chemicals including phthalates, pesticides, u.v.-filters, bisphenol A, parabens, and APAP. Following termination of dosing, animals were maintained on study and a subset of animals (male and female) from each dose group were assessed at later times for onset of puberty, estrous cyclicity, liver and reproductive tract histopathology, sperm count analysis, and hormonal levels. However, the study design employed does not address the potential for any association between prenatal exposure to APAP and development of ADHD in offspring.

Summary and Conclusions

The available nonclinical data from the published literature, reviewed previously by Dr. Mellon and colleagues (DAAAP) through publication year 2010 and since 2010 herein, do not describe studies in animals that were adequately designed and conducted to address the question posed by OSE. That question relates to reports from the clinical literature suggesting a potential association between consumption of APAP by women during pregnancy and a diagnosis of ADHD in their offspring. However, while the

potential may exist that adequately designed and conducted studies (pre-/postnatal studies and studies in sufficiently young juvenile animals) that include assessments of appropriate neurobehavioral/learning and memory endpoints may in the future be able to more thoroughly dimension the strength of any such association, at this time the behavioral responses in animals that are most likely to be predictive of an ADHD response in humans are uncertain and, therefore, additional animal studies are not likely to be informative.

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/s/

DONALD C THOMPSON
02/08/2016

PAUL C BROWN
02/08/2016